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EVALUATING LIFE TIME IN A COMPETING RISKS MODEL FOR A CHRONIC DISEASE

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1. Introduction

This paper aims at evaluating the (stochastic) life time of a subject confronted with the possibility of developing a chronic noncommunicable disease, such as cardiovascular diseases and cancer. To this end expected life time and expected utility of life time are used. These measures are planned to be used in evaluating a so called intervention program aimed at reducing the incidence of the disease.

In Section 2 the illness-death model, used to describe the various states from a disease free state towards the final state of death, is presented. Section 3 is concerned with life expectancy and a decomposition of life expectancy which is useful for evaluating an intervention program. In Section 4 form and construction of an individual utility function are discussed. Also in Section 4 the actual computation of expected utility is presented. Section 5 formulates the problem of when and how to intervene as a problem of maximizing expected utility.

2. The illness-death model

At any time the subject considered is in one of the mutually exclusive states of Figure 1.

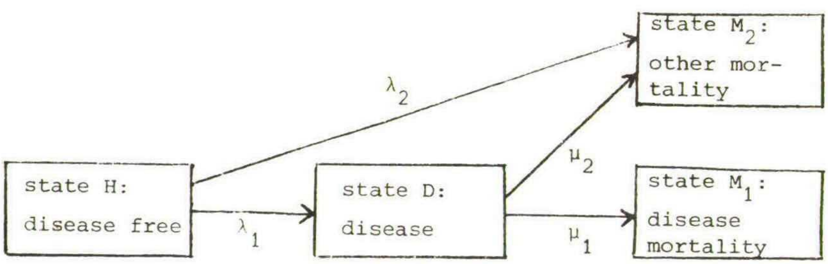

Figure 1. The illness-death model.

The subject is either dead or alive. In the latter case he is in one of the following two states:

state H: the disease free ("health") state, which applies if the disease has as yet not developed;

state D: the state of chronic disease, which applies as soon as the disease starts to develop.

When the subject dies, he dies either from the disease or from other causes. In the latter case he was either in state H or in state D, previous to the time of his death. Hence the following mortality states are considered:

state M_1: the state of mortality caused by the disease;

state M_2: the state of mortality caused by other diseases, which is reached from states H or D.

It remains to specify the failure rate functions of the competing risks. Time x is supposed to coïncide with age. The disease free state H can be left as a result of two competing risk causes: either the start of the disease with rate $\lambda_1(x)$, or mortality from other diseases with rate $\lambda_2(x)$. Return to the disease free state H is impossible. The disease state D can also be left as a result of two competing risk causes: either mortality from the disease with rate $\mu_1(x-t)$, with t the starting time of the disease, or mortality from other diseases with rate $\mu_2(x)$.

This completes the description of the illness-death process. Similar models may be found in Sacks and Chiang (1977), Sander (1978) and Beck (1979). In the next section the expected life time for this model and a relevant decomposition of expected life time is presented.

3. Life expectancy and its decomposition

Life expectancy is equal to the weighted mean of life expectancy given the subject considered develops the disease and of life expectancy given the subject does not develop the disease, with weights π_1 and $\pi_2 = 1-\pi_1$, where π_1 is the probability that the subject develops the disease and π_2 is the probability that the subject dies from other diseases.

Life expectancy, given no development of the disease, is calculated as follows. Let $\bar{F}_H(x)$ denote the so called survival function for the disease free state H, i.e. $\bar{F}_H(x)$ is the probability that the subject considered is (survives) in state H at time x. $\bar{F}_H(x)$ can be expressed in the parameters λ_1 and λ_2 as follows:

$$(3.1) \qquad \bar{F}_H(x) = \exp\left[-\int_0^x \{\lambda_1(y) + \lambda_2(y)\}dy\right].$$

The conditional density function of time x, given "failure" from cause j (j = 1,2), is:

$$(3.2) \qquad f_j(x) = \frac{\lambda_j(x)\bar{F}_H(x)}{\pi_j} \qquad (j = 1,2);$$

see e.g. David and Moeschberger (1978) and Kalbfleisch and Prentice (1980). Evidently π_j equals:

$$(3.3) \qquad \pi_j = \int_0^\infty \lambda_j(x)\bar{F}_H(x)\,dx \qquad (j = 1,2).$$

Life expectancy, given no development of the disease, to be denoted by $E(X|2)$, is equal to:

$$(3.4) \qquad E(X|2) = \int_0^\infty x\, f_2(x)\,dx.$$

Life expectancy, given (development of) the disease, equals the sum of life expectancy in the health state H given the disease and life expectancy in the disease state D. Life expectancy in state H, given development of the disease, denoted as $E(X|1)$, equals:

$$(3.5) \qquad E(X|1) = \int_0^\infty x\, f_1(x)dx.$$

Life expectancy in state D, denoted as $E(Z)$, equals:

$$(3.6) \qquad E(Z) = \int_0^\infty \int_0^\infty z\, f_1(x)g(z|x)\,dx\, dz,$$

where $g(z|x)$ is the conditional density function of z, life time with the disease, given that x is the starting time of the disease. This conditional density is derived from $\bar{F}_D(z|x)$, the conditional survival function for the disease state D, given x as starting time of the disease. Analogously to (3.1), $\bar{F}_D(z|x)$ is expressed as follows:

$$(3.7) \qquad \bar{F}_D(z|x) = \exp\left[-\int_0^z \{\mu_1(y) + \mu_2(x+y)\}dy\right].$$

From (3.7) one derives $g(z|x)$ as $-d\bar{F}_D/dz$:

$$(3.8) \qquad g(z|x) = \{\mu_1(z) + \mu_2(x+z)\}\bar{F}_D(z|x).$$

Life expectancy, given development of the disease, thus is the sum of (3.5) and (3.6).

Life expectancy E thus equals:

$$(3.9) \qquad E = \pi_1\{E(X|1) + E(Z)\} + (1-\pi_1)E(X|2),$$

with $E(X|1)$, $E(X|2)$ and $E(Z)$ defined in (3.5), (3.4) and (3.6). The decomposition of E in the right hand side of (3.9), illustrated in Figure 2, is useful for evaluating so called intervention programs aiming at reducting the incidence of the disease, $\lambda_1(x)$. It clearly shows the several possible effects to intervention: a change in λ_1, induced by manipulating its influencing variables (see Kalbfleisch and Prentice (1980)) results in changes in the disease probability π_1 and in the expectations $E(X|1)$, $E(X|2)$ and $E(Z)$.

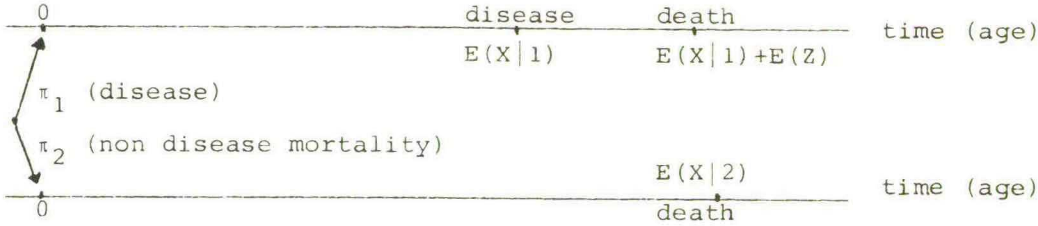

Figure 2. Decomposition of life expectancy.

4. Expected utility

Life expectancy E is one evaluation parameter for the illness-death process. It does not define uniquely all situations of an illness-death process between which a subject may be indifferent. For instance, a second process with a higher value of $E(X|2)$, that is exactly cancelled out by a lower value of $E(Z)$, produces the same value of E, while it is reasonable to assume that this second process is preferred by the subject over the first process. As the subject is facing changes, induced by intervention, of the stochastic illness-death process, the "rational" subject would not only look at expected life time, but also take the more general approach of calculating expected utilities of life times of two different processes.

A particular illness-death process can be described by the following joint density function of the triplet (X,W,J), with X desease free life time, W disease duration and J an indicator for the disease, having the value 1 if the disease develops and 2 if not:

$$
\begin{aligned}
(4.1) \qquad h(x,w,j) &= \pi_1 f_1(x) g(w|x) && \text{for } x \geq 0,\ w > 0,\ j = 1 \\
&= (1-\pi_1) f_2(x) && \text{for } x \geq 0,\ w = 0,\ j = 2 \\
&= 0 && \text{otherwise,}
\end{aligned}
$$

as follows from the previous section. The random variable W coïncides with the random variable Z of the previous section except that for w = 0 there is a probability mass of $1-\pi_1$. The parameters λ_1, λ_2, μ_1 and μ_2 determine $h(x,w,j)$.

The subject is assumed to evaluate changes in $h(x,w,j)$, induced for example by certain intervention measures, by means of his expected utility of the triplet (X,W,J). The utility function U is defined as $u(x)$ for a disease free life time of x time units and as $v'(x,w)$ for a life time in which the disease starts to develop at time x and lasts for w time units. So formally U is defined as:

$$(4.2) \qquad U(x,w,j) = (j-1)u(x) + (2-j)v'(x,w).$$

Expected utility equals:

$$(4.3) \qquad E\{U(X,W,J)\} = (1-\pi_1)E\{u(X)\,|\,J = 2\} + \pi_1 E\{v'(X,W)\,|\,J=1\}.$$

For the sequel $v'(x,w)$ is assumed to be as follows:

$$(4.4) \qquad v'(x,w) = u(x) + v(x,w)$$

i.e. the utility of a life time w with the disease, which started at time x, may be separately added to the utility of the disease free time of life. The utility function then becomes:

$$(4.5) \qquad U(x,w,j) = u(x) + (2-j)v(x,w),$$

with expectation:

$$(4.6) \qquad E\{U(X,W,J)\} = E\{u(X)\} + \pi_1 E\{v(X,W)\,|\,J = 1\}.$$

Using (4.1) in (4.6) gives:

$$(4.7) \qquad E(U) = \int_0^\infty u(x)\{\pi_1 f_1(x) + (1-\pi_1)f_2(x)\}dx + \\ + \pi_1 \int_0^\infty \int_0^\infty v(x,z)f_1(x)g(z|x)dx\,dz,$$

which for computational purposes may be rewritten as:

$$(4.8) \qquad E(U) = -\int_0^\infty u(x)\,d\bar{F}_H - \int_0^\infty \lambda_1(x)\bar{F}_H(x)\{\int_0^\infty v(x,z)\,d\bar{F}_D(z|x)\}dx.$$

Integrating (4.8) by parts results in:

$$(4.9) \qquad E(U) = \int_0^\infty u_x\bar{F}_H(x)\,dx + \int_0^\infty \lambda_1(x)\bar{F}_H(x)\{\int_0^\infty v_z\bar{F}_D(z|x)\,dz\}dx,$$

where $u_x = du/dx$ and $v_z = \partial v/\partial z$ are marginal utilities and where it has been assumed that $u(x)\bar{F}_H(x) \to 0$ as $x \to \infty$ and $v(x,z)\bar{F}_D(z|x) \to 0$ as $z \to \infty$.
The usefulness of (4.9) will become clear after more has been said about the specification of $u(x)$ and $v(x,z)$.

In order to specify the utility function further, it is supposed that the subject is able to compare his various health conditions. Two assumedly independent types of health conditions are distinguished: a general health condition related to all kinds of diseases other than the one considered and a (disease) specific health condition. The subject is supposedly able to compare his general health condition at one age with that at another age, and to compare his specific health condition with the general health condition for any given age and disease duration.

Let $q(y)$ denote the general health index at age y. $q(y)$ assumedly is a non-negative number, that is equal to 1 at age y^* of maximal general health condition. The function $q(y)$ can be determined from the subject's stated indifference between one unit of life time at age y (without the disease) and $q(y)/q(y^*) = q(y)$ units of life time at age y^*, for all pairs (y,y^*). The subject's use for a life time x without the disease is by reasonable assumption equal to the sum (integral) of his successive health conditions, starting from time 0 (which generally is not his time of birth):

$$(4.10) \qquad u(x) = \int_0^x q(y)\,dy.$$

With this construction of $u(x)$, it follows for marginal utility:

$$(4.11) \qquad \frac{du}{dx} = q(x).$$

Further, let $q_D(y)$ denote the specific health index for a subject already having the disease for a time period of y. Without loss of generality, it is assumed that $q_D(y)$ has a maximum of 1. The time x of the start of the disease is introduced as follows. The general health condition at time x+y is represented by the value $q(x+y)$, which value is assumed to act multiplicatively on $q_D(y)$ in order to produce the overall health index at time x+y, with value $q(x+y)q_D(y)$. The subject's use for a life time z with the disease, which started at time x, is by assumption equal to the sum (integral) of his successive overall health conditions, starting from time x:

$$(4.12) \qquad v(x,z) = \int_0^z q(x+y)q_D(y)\,dy.$$

With this construction of $v(x,z)$ it follows that:

$$(4.13) \qquad \frac{\partial v(x,z)}{\partial z} = q(x+z)q_D(z).$$

Returning to $E(U)$ in (4.9), it is seen that, given the above construction of $u(x)$ and $v(x,z)$, u_x and v_z in (4.9) may be replaced by (4.11) and (4.13), respectively.

The special case $q(x) = q_D(z) = 1$, meaning that the subject experiences constant marginal utilities, so that $u(x) = x$ and $v(x,z) = z$, specifies the case of the previous section, i.e. life expectancy E; see (4.7). In order to compute E numerically one may use (4.9) with $u_x = v_z = 1$.

An analogous decomposition as of life expectancy, may be effectuated for expected utility. This follows from (4.7) which for the purpose of actually computing the several components may be written as:

$$(4.14)\qquad E(U) = \pi_1 E\{u(X)\,|\,J=1\}+\pi_1 E\{v(X,Z)\,|\,J=1\}+(1-\pi_1)E\{u(X)\,|\,J=2\}$$

$$= \int_0^\infty u(x)\lambda_1(x)\bar{F}_H(x)\,dx+\int_0^\infty \lambda_1(x)\bar{F}_H(x)\{\int_0^\infty v_z \bar{F}_D(z\,|\,x)\,dz\}dx+$$

$$+ \int_0^\infty u(x)\lambda_2(x)\bar{F}_H(x)\,dx,$$

which, setting $u(x) = x$ and $v_z = 1$, may also be used to actually compute the components of life expectancy E.

An example of a general health index $q(x)$ is:

$$(4.15)\qquad q(x) = e^{-rx},$$

specifying that the general health condition is at its maximum at age 0 and decreases at rate r, due to the increasing prevalence of the other diseases. The utility $u(x)$ of a disease free life time from 0 to x then becomes:

$$(4.16)\qquad u(x) = \int_0^x e^{-ry}dy = \frac{1}{r}(1-e^{-rx}),$$

with $u(x) \to 1/r$ as $x \to \infty$.

Two examples of a (disease) specific health index are:

$$(4.17a)\qquad q_D(z) = e^{-sz}$$

$$(4.17b)\qquad q_D(z) = 1 - \{1-q_D(0)\}e^{-sz}.$$

The index (4.17a) specifies a disease that becomes more serious with the duration of the disease. It implies that, from the start of the disease at age x, the overall health index at time $y > x$ is $q(y)\exp\{-s(y-x)\}$. The index (4.17b) specifies a disease that becomes less serious with the disease duration. It implies that, at the start of the disease at age x, the overall health index decreases by an amount $q(x)q_D(0)$, while at time $y > x$ it decreases by an amount $q(y)q_D(0)\exp\{-s(y-x)\}$.

5. The intervention decision problem

From a decision maker's point of view the utility of some individual's life time could differ from the individual's own specification. For example: $q(x) = \exp\{-r'|x-40|\}$, which specifies that a disease free 40 year old subject has, to the decision maker's point of view, maximal utility.

Another complication, when imaging a decision maker's point of view, is that a decision maker will not consider one subject at a time, but all subjects simultaneously. Assuming identical utility functions, the problem of averaging the individual expected utility functions has its simplest representation in the following expression for the average expected utility:

$$(5.1) \qquad E_C\,[E\{U(X,W,J)\,|\,C = c\}]\,,$$

where C is a vector of (once measured) covariables (with a given distribution over the population of subjects), supposedly determining the time path of the rates λ_1 and λ_2. Average expected utility (5.1) (and thus average life expectancy) may be approximated by Monte Carlo simulation, as follows: make a sufficient number of random drawings from the distribution of C; determine the rates λ_1 and λ_2; calculate the expected utilities $E\{U(X,W,J)\,|\,c\}$ from (4.9) or (4.14) for each vector c drawn and average the expected utilities.

A more complicated but also more realistic approach is as follows: λ_1 and λ_2 are constant in predetermined periods (say 1,2,...), while the level of λ_1 and λ_2 in period t depends on the value of a vector of covariables measured at the start of period t. The vector C in (5.1) then consists of vectors of covariables supposedly measured at the starts of periods 1,2,... in a disease free subject. This newly defined vector C now determines the time path of λ_1 and λ_2. The simulation of average expected utility (5.1) is somewhat more complicated as a dynamic element is introduced: the distribution of covariables evolves over time.

The intervention problem may be defined by means of (5.1): choose the time $t < x$ of screening the disease free subjects (i.e. measure the relevant covariables, giving the vector c, at age t) and take some appropriate action a(c) from the set of possible actions, such that (5.1) is maximal. The action a(c), which depends on c, is designed to influence c to a new, more desired, value, giving a new time path for λ_1 and λ_2 from time t on.

A refinement may be accomplished by incorporating the action a(c) as an argument in the utility function. After all, the result of intervention may be the start of some form of treatment of a subject, meaning that the subject becomes a patient for the rest of his disease free life. Analogously to the disease specific health index $q_D(.)$, an <u>action specific health index</u> $q_a(.)$ may be defined on which the general health index $q(.)$ acts multiplicatively.

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